Missense Mutations in Plakophilin-2 Cause Sodium Current Deficit and Associate with a Brugada Syndrome Phenotype.

Journal: Circulation

Publication Year: 2013

Authors: Marina Cerrone, Xianming Lin, Mingliang Zhang, Esperanza Agullo-Pascual, Anna Pfenniger, Halina Chkourko-Gusky, Valeria Novelli, Changsung Kim, Tiara Tirasawadichai, Daniel P Judge, Eli Rothenberg, Huei-Sheng Vincent Chen, Carlo Napolitano, Silvia Priori, Mario Delmar

PubMed link: 24352520

Funding Grants: Development of Neuro-Coupled Human Embryonic Stem Cell-Derived Cardiac Pacemaker Cells., Endothelial cells and ion channel maturation of human stem cell-derived cardiomyocytes, Studying Arrhythmogenic Right Ventricular Dysplasia with patient-specific iPS cells

Public Summary:
Brugada syndrome (BrS) is a inherited disease that can cause sudden death in the young people (<35 years old). This heart disease primarily associates with loss of sodium channel function. one type of heart cell-cell junctional proteins is named desmosome. Previous studies showed inherited mutations in desmosomal proteins lead to sodium current deficits in hearts of patients diagnosed with arrhythmogenic cardiomyopathy (or arrhythmogenic right ventricular dysplasia/ cardiomyopathy). Several experimental models have showed correlation between loss of expression of desmosomal protein plakophilin-2 (PKP2) and reduced sodium currents. In this study, we identified 5 patients with PKP2 mutations from 200 patients with Brugada syndrome. These 5 patients have no other known Brugada-linked genetic muations. We found that the sodium currents are small in a mouse atrial cell line and in a human ARVD/C patient-specific stem cell line that have defective PKP2. Wild-type PKP2, but not Brugada mutant PKP2, can rescue their sodium channel deficits. Super-resolution microscopy in mouse PKP2-deficient heart cells related sodium current deficiency to the reduced number of sodium channels at a specific cell-cell junction and to increased separation of microtubules from the cell-end. This is the first systematic retrospective analysis of a patient group to define the co-existence of sodium channel deficits and genetic PKP2 variations. PKP2 mutations may be a molecular substrate leading to the diagnosis of Brugada syndrome.

Scientific Abstract:
BACKGROUND: Brugada syndrome (BrS) primarily associates with loss of sodium channel function. Previous studies showed features consistent with sodium current (INa) deficit in patients carrying desmosomal mutations, diagnosed with arrhythmogenic cardiomyopathy (AC; or arrhythmogenic right ventricular cardiomyopathy, ARVC). Experimental models showed correlation between loss of expression of desmosomal protein plakophilin-2 (PKP2), and reduced INa. We hypothesized that PKP2 variants that reduce INa could yield a BrS phenotype, even without overt structural features. METHODS AND RESULTS: We searched for PKP2 variants in genomic DNA of 200 patients with BrS diagnosis, no signs of AC, and no mutations in BrS-related genes SCN5A, CACNa1c, GPD1L and MOG1. We identified 5 cases of single amino acid substitutions. Mutations were tested in HL-1-derived cells endogenously expressing NaV1.5 but made deficient in PKP2 (PKP2-KD). Loss of PKP2 caused decreased INa and NaV1.5 at site of cell contact. These deficits were restored by transfection of wild-type PKP2 (PKP2-WT), but not of BrS-related PKP2 mutants. Human induced pluripotent stem cell cardiomyocytes (hIPSC-CMs) from a patient with PKP2 deficit showed drastically reduced INa. The deficit was restored by transfection of WT, but not BrS-related PKP2. Super-resolution microscopy in murine PKP2-deficient cardiomyocytes related INa deficiency to reduced number of channels at the intercalated disc, and increased separation of microtubules from the cell-end. CONCLUSIONS: This is the first systematic retrospective analysis of a patient group to define the co-existence of sodium channelopathy and genetic PKP2 variations. PKP2 mutations may be a molecular substrate leading to the diagnosis of BrS.

associate